Claims.

What is claimed is:

1. A transgenic non-human mammal, wherein the mammal carries a targeted disruption in the coding sequence of an endogenous surfactant protein C (SP-C) gene and wherein the targeted disruption inhibits production of wild-type surfactant protein C so that the phenotype of the mammal is characterized by a pulmonary disorder condition consistent with changes in humans with familial SP-C deficiency.

2. The transgenic mammal of claim 1, wherein the mammal develops a severe progressive pulmonary disorder with histologic features consistent with interstitial pneumonitis.

3. The transgenic mammal of claim 2, wherein the phenotype of the mammal comprises at least one phenotype selected from the group consisting of emphysema, monocytic infiltrates, fibrosis, epithelial cell dysplasia, and atypical accumulations of intracellular lipids in type II epithelial cells and alveolar macrophages.

4. The transgenic mammal of claim 3, wherein the pulmonary disorder condition is consistent with changes in humans with familial SP-C deficiency.

5. The transgenic mammal of claim 4, wherein the mammal is heterozygous for the disruption in the surfactant protein C gene.

6. The transgenic mammal of claim 4, wherein the mammal is homozygous for the targeted disruption in the surfactant protein C gene.

7. The transgenic mammal of claim 4, wherein the phenotype includes damage to the lung tissue.

8. The transgenic mammal of claim 4, wherein the mammal is a mouse.

9. The transgenic mouse of claim 8, wherein the mouse is derived from a 129/Sv mouse line.

10. The transgenic mouse of claim 8, wherein the disruption is created by insertional disruption of exon 2.

11. The transgenic mouse of claim 8, wherein the targeted disruption includes at least nucleotide position 1667 at the ApaL1 site in exon 2 of the wild type surfactant protein C gene.

12. The transgenic mammal of claim 4, wherein the disruption is created by a deletion of at least 50 consecutive nucleotides of coding sequence of the surfactant protein C gene.

13. A cell or cell line from a transgenic mouse, wherein the cell or cell line contains a targeted disruption in the coding sequence of an endogenous surfactant protein C (SP-C) gene.

14. The cell or cell line of claim13, wherein the mouse is derived from a 129/Sv mouse line.

15. The cell or cell line of claim 13, wherein the disruption is created by insertional disruption of exon 2.

16. The cell or cell line of claim 15, wherein the disruption includes at least nucleotide position 1667 at the ApaL1 site in exon 2 of the wild type surfactant protein C gene.

17. The cell or cell line of claim 13, wherein the targeted disruption is created by a deletion of at least 50 consecutive nucleotides of coding sequence of the surfactant protein C gene.

18. The cell or cell line of claim 13, which is an undifferentiated cell.

19. The cell or cell line of claim 14, wherein the undifferentiated cell is selected from the group consisting of a stem cell, embryonic stem cell oocyte and embryonic cell.

20. A method of producing a mouse with a targeted disruption in a surfactant protein C (SP-C) gene, comprising the steps of:

    a. creating a knockout construct comprising a portion of the SP-C gene with an internal portion of said SP-C gene replaced by a

marker, wherein at least 50 consecutive nucleotides of SP-C gene coding sequence have been deleted;

b. transfecting said knockout construct into a population of embryonic stem cells and selecting a transfected ES cell which expresses said marker;

c. introducing said transfected ES cell into an embryo of an ancestor of said mouse;

d. allowing said embryo to develop to term to produce a chimeric mouse with the knockout construct in its germline;

e. breeding said chimeric mammal, to produce a heterozygous mouse with a targeted disruption in the SP-C gene.

21. An surfactant protein C knock-out construct, comprising a portion of an surfactant protein C (SP-C) gene, wherein an internal portion of said SP-C gene is replaced by a selectable marker and at least 50 consecutive nucleotides of SP-C gene coding sequence have been deleted.

22. The SP-C knockout construct of claim 21, wherein the selectable marker is a gene encoding a protein selected from the group consisting of thymidine kinase, neomycin phosphotransferase and hygromycin B phosphotransferase.

23. The SP-C knock-out construct of claim 21, wherein the marker is a neomycin resistance gene.

24. A method of testing an agent for effectiveness against a pulmonary condition, said method comprising:

a. obtaining a transgenic mouse that is homozygous for an surfactant protein C null allele wherein the transgenic mouse exhibits a phenotype selected from the group consisting of emphysema, monocytic infiltrates, fibrosis, epithelial cell dysplasia, and

atypical accumulations of intracellular lipids in type II epithelial cells and alveolar macrophages, and

b. administering said agent to said transgenic animal;

wherein an agent that ameliorates said phenotype is selected as an agent that has effectiveness against said condition.

25. The method of claim 20, wherein the ancestor of said mouse is a 129/Sv mouse.

26. The method of claim 24, wherein the mouse is derived from a 129/Sv mouse line.

27. The method of claim 24, wherein the surfactant protein C null allele is created by a targeted disruption in the coding sequence of an endogenous surfactant protein C (SP-C) gene.

28. The method of claim 24, wherein the surfactant protein C null allele is created by insertional disruption of exon 2.

29. The method of claim 24, wherein the disruption includes at least nucleotide position 1667 at the ApaL1 site in exon 2 of the wild type surfactant protein C gene.

30. The method of claim 24, wherein the surfactant protein C null allele is created by a deletion of at least 50 consecutive nucleotides of coding sequence of the surfactant protein C gene.

31. The transgenic mammal of claim 4, wherein the mammal is an SP-C knockout mouse.

32. The transgenic mammal of claim 31, wherein the mammal is a proSP-C knockout.

33. The transgenic mammal of claim 4, wherein the mammal does not express SP-C.

34. The transgenic mammal of claim 4, wherein the mammal does not express active SP-C.

35. The method of claim 24 wherein the mouse is an SP-C knockout mouse.

36. The method of claim 35 wherein the mouse is a proSP-C knockout.

37. The method of claim 24 wherein the mouse does not express SP-C.

38. The method of claim 24 wherein the mouse does not express active SP-C.

39. A method of treating pulmonary disease in a subject comprising the administration to a subject in need of such treatment a therapeutically effective amount of a formulation comprising a SP-C therapeutic.

40. The method of claim 1 wherein the SP-C therapeutic is an agent selected from the group consisting of an isolated SP-C protein, an isolated nucleic acid molecule encoding a SP-C protein, a SP-C receptor-specific antibody that stimulates the activity of the receptor, or pharmaceutically acceptable composition thereof.

41. The method of claim 40, wherein the SP-C therapeutic agent is a SP-C receptor-specific antibody that stimulates the activity of the receptor..

42. The method of claim 40, wherein the SP-C therapeutic agent is an isolated SP-C protein or proSP-C protein.

43. The method of claim 40, wherein the SP-C therapeutic agent is an isolated nucleic acid molecule encoding a SP-C protein or proSP-C protein, wherein the nucleic acid molecule is operatively linked to a transcription control sequence.

44. The method of claim 43, wherein the nucleic acid molecule is expressed in the subject's airway cells.

45. The method of claim 44, wherein the nucleic acid that encodes a SP-C polypeptide, fragment, homolog or variant with substantial homology, supplying SP-C function.

46. The method of claim 45, wherein the nucleic acid molecule becomes integrated to the chromosomal DNA making up the genome of the subject's airway cells.

47. The method of claim 45, wherein the nucleic acid molecule is expressed by the subject's airway cells from an extrachromosomal location.

48. The method of claim 45, wherein the nucleic acid molecule comprises at least 50 nucleotides.

49. The method of claim 45, wherein the nucleic acid molecule comprises at least 200 nucleotides.

50. The method of claim 45, wherein the airway cells are selected from the group consisting of smooth muscle and epithelial cells.

51. The method of claim 45, wherein the isolated nucleic acid molecule is administered to the mammal complexed with a liposome delivery vehicle.

52. The method of claim 45, wherein the isolated nucleic acid molecule is administered to the mammal in a viral vector delivery vehicle.

53. The method of claim 52, wherein the viral vector delivery vehicle is from adenovirus.

54. The method of claim 45, wherein the isolated nucleic acid molecule, when administered to the lungs of the mammal, is expressed in cells of the mammal.

55. The method of claim 40, wherein the disease is a chronic obstructive pulmonary disease of the airways associated with eosinophilic inflammation.

56. The method of claim 40, wherein the disease is selected from the group consisting of airway obstruction, allergies, asthma, acute inflammatory lung disease, chronic inflammatory lung disease, chronic obstructive pulmonary dysplasia, emphysema, pulmonary emphysema, chronic obstructive emphysema, adult respiratory distress syndrome, bronchitis, chronic bronchitis, chronic asthmatic bronchitis, chronic obstructive bronchitis, and interstitial lung diseases.

57. The method of claim 40, wherein the SP-C therapeutic agent decreases lung inflammation in the mammal.

58. The method of claim 40, wherein the SP-C therapeutic agent is administered in an amount between about 0.1 micrograms/kilogram and about 10 milligram/kilogram body weight of a mammal.

59. The method of claim 40, wherein the SP-C therapeutic agent is administered in a pharmaceutically acceptable excipient.

60. The method of claim 40, wherein the mammal is a human.

61. The method of claim 1, wherein the SP-C therapeutic agent is administered by at least one route selected from the group consisting of nasal and inhaled routes.

62. The method of claim 40, wherein the pulmonary disease is selected from the group consisting of asthma, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonia, eosinphilic pneumonia, allergic bronchitis bronchiectasis, hypersensitivity pneumotitis, occupational asthma, reactive airway disease syndrome, hypereosinophilic syndrome, rhinitis, sinusitis, and parasitic lung disease.

63. A method for prescribing treatment for airway hyperresponsiveness and/or airflow limitation associated with a respiratory disease involving an inflammatory response in a mammal, comprising: a. administering to the lungs of a mammal a SP-C therapeutic agent selected from the group consisting of: a SP-C receptor-specific antibody that stimulates the activity of the receptor an isolated SP-C protein or proSP-C protein; and an isolated nucleic acid molecule encoding a SP-C protein or proSP-C protein, wherein the nucleic acid molecule is operatively linked to a transcription control sequence; b. measuring a change in lung function in response to a provoking agent in the mammal to determine if the SP-C therapeutic agent modulates airway hyperresponsiveness; and c. prescribing a pharmacological therapy

comprising administration of SP-C therapeutic agent to the mammal effective to reduce inflammation based upon the changes in lung function.

64. A formulation for protecting a mammal from airway hyperresponsiveness, airflow limitation and/or airway fibrosis associated with a respiratory disease involving inflammation, comprising an anti-inflammatory agent effective for reducing eosinophilic inflammation and a SP-C therapeutic agent selected from the group consisting of: a SP-C receptor-specific antibody that stimulates the activity of the receptor; an isolated SP-C protein or proSP-C protein; and an isolated nucleic acid molecule encoding a SP-C protein or proSP-C protein, wherein the nucleic acid molecule is operatively linked to a transcription control sequence.

65. The formulation of claim 64, wherein the formulation comprises a pharmaceutically acceptable excipient.

66. The formulation of claim 64, wherein the formulation comprises a controlled release vehicle selected from the group consisting of biocompatible polymers, other polymeric matrices, capsules, microcapsules, microparticles, bolus preparations, osmotic pumps, diffusion devices, liposomes, lipospheres, viral vectors and transdermal delivery systems.

67. The formulation of claim 64, wherein the SP-C therapeutic agent is an isolated SP-C protein or proSP-C protein.

68. The formulation of claim 64, wherein the SP-C therapeutic agent is an isolated nucleic acid molecule encoding a SP-C protein or proSP-C protein, wherein the nucleic acid molecule is operatively linked to a transcription control sequence.

69. The formulation of claim 68, wherein the isolated nucleic acid molecule is complexed with a liposome delivery vehicle.

70. The formulation of claim 68, wherein the isolated nucleic acid molecule in a viral vector delivery vehicle.

71. The formulation of claim 70, wherein the viral vector delivery vehicle is from adenovirus.

72. The formulation of claim 64, wherein the SP-C therapeutic agent is a SP-C receptor-specific antibody that stimulates the activity of the receptor.

73. The formulation of claim 64, wherein the SP-C therapeutic agent is selected from the group consisting of: an isolated SP-C protein or proSP-C protein and an isolated nucleic acid molecule encoding a SP-C protein or proSP-C protein, wherein the nucleic acid molecule is operatively linked to a transcription control sequence.

74. The formulation of claim 64, wherein the anti-inflammatory agent is selected from the group consisting of anti-IgE, immunomodulating drugs, leukotriene synthesis inhibitors, leukotriene receptor antagonists, glucocorticosteroids, steroid chemical derivatives, anti-cyclooxygenase agents, beta-adrenergic agonists, methylxanthines, cromones, anti-CD4 reagents, anti-IL-5 reagents, surfactants, cytoxin, and heparin.

75. The formulation of claim 64, wherein the anti-inflammatory agent is selected from the group consisting of leukotriene synthesis inhibitors, leukotriene receptor antagonists, glucocorticosteroids, beta-adrenergic agonists, methylxanthines, and cromones.